

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-11 (cancelled).

12 (currently amended). An isolated polypeptide comprising an ~~or essentially consisting of~~ the amino acid sequence having at least 75% sequence identity with a reference sequence which is of SEQ ID NO:2, or a fragment thereof, wherein said polypeptide, and, if said reference sequence is a fragment, said fragment,

- i) has a proteolytic activity specific at least for Insulin Like Growth Factor Binding Protein 5 (IGFBP-5); and/or
- ii) is recognised by an antibody, or a binding fragment thereof, ~~which is capable of recognising~~ recognizes a polypeptide having the amino acid sequence as shown in SEQ ID NO:2; and/or
- iii) competes with a polypeptide having the amino acid sequence as shown in SEQ ID NO:2 for binding to a cell surface receptor with an affinity for said polypeptide.

13 (currently amended). Polypeptide according to claim 12, wherein the reference sequence is a fragment which comprises ~~or essentially consists of~~ amino acid residues 234 to 1791 of SEQ ID NO:2, corresponding to the mature part of PAPP-A2, including any processing variant thereof.

14 (currently amended). Polypeptide according to claim 12, wherein the reference sequence is a fragment which comprises ~~or essentially consists of~~ amino acid residues 1 to 233 corresponding to the prepro part of PAPP-A2.

15 (currently amended). Polypeptide according to claim 12, wherein the reference sequence is a fragment which comprises ~~or essentially consists of~~ amino acid residues 23 to 233 of SEQ ID NO:2, corresponding to the pro part of PAPP-A2.

16 (currently amended). Polypeptide according to claim 12, wherein the reference sequence is a fragment which comprises ~~or essentially consists of~~ amino acid residues 1 to 22 of SEQ ID NO:2, corresponding to the signal peptide or leader sequence of PAPP-A2.

17 (currently amended). Polypeptide according to claim 14, wherein the prepro part of PAPP-A2 is operably linked to the mature part of PAPP-A2 corresponding to amino acid residues 234 to 1791 of SEQ ID NO:2.

18. (previously presented) Polypeptide according to claim 12, wherein said polypeptide is a recombinant polypeptide.

19. (previously presented) Polypeptide according to claim 12, wherein the polypeptide is free of human proteins, or other proteins natively associated with said polypeptide.

20-29 (cancelled).

30 (currently amended). A method for detecting PAPP-A2, or measuring the level of PAPP-A2, in a biological sample obtained from an individual, said method comprising the steps of

- i) obtaining a biological sample from said individual,
- ii) detecting PAPP-A2 in said sample by detecting
 - a) a polypeptide according to claim 12, ~~and/or~~
 - b) ~~a polynucleotide in the form of mRNA~~
~~originating from PAPP-A2 expression, and/or~~

~~e) PAPP-A2 specific protease activity, preferably by detecting cleavage of ICFBP-5, a derivative thereof, or any other suitable substrate for PAPP-A2.~~

31 (original). Method of claim 30, said method comprising the further step of comparing the PAPP-A2 or the level of PAPP-A2 detected in step ii) with a predetermined value selected from the group consisting of

- i) a predetermined amount and/or concentration of PAPP-A2; and/or
- ii) a predetermined amount and/or concentration of PAPP-A2 mRNA; and/or
- iii) a predetermined PAPP-A2 specific protease activity.

32 (original). Method of claim 31, wherein said predetermined value is indicative of a normal physiological condition of said individual.

33 (original). The method of claim 30, wherein said biological sample is selected from the group consisting of blood, urine, pleural fluid, oral washings, tissue biopsies, and follicular fluid.

34 (original). The method of claim 30, wherein said level of PAPP-A2 is measured as PAPP-A2 specific protease activity.

35 (original). The method of claim 30, wherein said level of PAPP-A2 is measured as amount of PAPP-A2 protein.

36 (original). The method of claim 30, wherein said level of PAPP-A2 is measured as amount of PAPP-A2 messenger RNA.

37 (original). The method of claim 35, wherein said amount of PAPP-A2 protein is measured by immunochemical analysis.

38 (original). The method of claim 37, wherein said amount of PAPP-A2 protein is detected by at least one monoclonal antibody.

39 (original). The method of claim 30, wherein said PAPP-A2 protein is detected in a complex comprising at least one additional component, preferably a polypeptide.

40 (original). The method of claim 30, wherein said PAPP-A2 is detected as a PAPP-A2 monomer.

41 (original). The method of claim 30, wherein said PAPP-A2 is detected as a PAPP-A2 dimer.

42 (previously presented). A method of diagnosing a clinical condition in an individual, said method comprising the steps of

- i) performing the method of claim 30, and
- ii) diagnosing the clinical condition.

43 (original). Method of claim 42, wherein said clinical condition is a fetal abnormality.

44 (original). The method of claim 43, wherein said fetal abnormality is selected from the group consisting of Trisomy 21, Trisomy 18, Trisomy 13, and Open Spina Bifida.

45 (original). The method according to claim 43, wherein said fetal abnormality is ectopic pregnancy, open spina bifida, neural tube defects, ventral wall defects, Edwards Syndrome, Patau's Syndrome, Turner Syndrome, Monosomy X or Klinefelter's Syndrome.

46 (original). The method of claim 43, wherein said clinical condition is an altered growth state selected from the group consisting of a growth promoting state and a growth inhibiting state.

47 (original). The method of claim 46, wherein said clinical condition is selected from the group consisting of restenosis, atherosclerosis, wound healing, fibrosis, myocardial infarction, osteoporoses, rheumatoroid arthritis, multiple myeloma, or cancer.

48 (cancelled).

49 (original). A method for identifying an agent inhibiting the protease activity of PAPP-A2, said method comprising the steps of

- i) incubating a) the polypeptide according to claim 12 and b) a predetermined substrate for said polypeptide, and c) a putative inhibitory agent, and
- ii) ~~determinining~~ determining if proteolysis of said substrate is inhibited.

50 (original). The method of claim 49, wherein said substrate comprises a polypeptide.

51 (original). The method of claim 50, wherein said substrate comprises an internally quenched fluorescent peptide.

52 (original). The method of claim 50, wherein said substrate comprises or essentially consists of IGFBP-5, or a fragment thereof.

53 (previously presented). An inhibitory agent obtainable according to the method of claim 49.

54 (cancelled).

55 (original). A method for identifying an agent enhancing the protease activity of PAPP-A2, said method comprising the steps of

- i) incubating a) the polypeptide according to claim 12 and b) a predetermined substrate for said polypeptide, and c) a putative enhancer agent, and

ii) determining if proteolysis of said substrate is enhanced.

56 (currently amended). The method of claim ~~53~~ 55, wherein said substrate comprises a polypeptide.

57 (currently amended). The method of claim ~~54~~ 55, wherein said substrate comprises an internally quenched fluorescent peptide.

58 (currently amended). The method of claim ~~54~~ 55, wherein said substrate comprises or essentially consists of IGFBP-5, or a fragment thereof.

59 (previously presented). An enhancing agent obtainable according to the method of claim 54.

60-61 (cancelled).

62 (original). A method for purification of PAPP-A2 or complexes of PAPP-A2 with other proteins, said method comprising the steps of

- i) providing a polyclonal or monoclonal antibody with specific binding affinity for a polypeptide according to claim 12,
- ii) purifying PAPP-A2 by means of affinity chromatography.

63-69 (cancelled).

70 (new). The polypeptide of claim 12 wherein said polypeptide is SEQ ID NO:2, or a fragment thereof.

71 (new). The polypeptide of claim 12 comprising an amino acid sequence having at least 80% sequence identity with said reference sequence.

72 (new). The polypeptide of claim 12 comprising an amino acid sequence having at least 85% sequence identity with said reference sequence.

73 (new). The polypeptide of claim 12 comprising an amino acid sequence having at least 90% sequence identity with said reference sequence.

74 (new). The polypeptide of claim 12 comprising an amino acid sequence having at least 95% sequence identity with said reference sequence.

75 (new). The polypeptide of claim 12 comprising an amino acid sequence having at least 98% sequence identity with said reference sequence.

76 (new). The polypeptide of claim 12 in which the reference sequence comprises AAs 234 to 1791 of SEQ ID NO:2.

77 (new). The polypeptide of claim 70 in which the reference sequence comprises AAs 234 to 1791 of SEQ ID NO:2.

78 (new). The polypeptide of claim 71 in which the reference sequence comprises AAs 234 to 1791 of SEQ ID NO:2.

79 (new). The polypeptide of claim 72 in which the reference sequence comprises AAs 234 to 1791 of SEQ ID NO:2.

80 (new). The polypeptide of claim 73 in which the reference sequence comprises AAs 234 to 1791 of SEQ ID NO:2.

81 (new). The polypeptide of claim 74 in which the reference sequence comprises AAs 234 to 1791 of SEQ ID NO:2.

82 (new). The polypeptide of claim 75 in which the reference sequence comprises AAs 234 to 1791 of SEQ ID NO:2.

83 (new). The polypeptide of claim 12 which comprises an amino acid sequence which differs from said reference sequence solely by one or more conservative substitutions.

84 (new). The polypeptide of claim 83 in which said reference sequence is amino acids 234 to 1791 of SEQ ID NO:2.

85 (new). The polypeptide of claim 12 which comprises an amino acid sequence which is identical to amino acids 234 to 1791 of SEQ ID NO:2.

86 (new). The polypeptide of claim 12 which consists essentially of amino acids 234 to 1791 of SEQ ID NO:2.

87 (new). The polypeptide of claim 12 which consists of amino acids 234 to 1791 of SEQ ID NO:2.

88 (new). The polypeptide of claim 12 which comprises a segment of at least 7 amino acids which is identical to an equal length segment within amino acids 234 to 1791 of SEQ ID NO:2.

89 (new). The polypeptide of claim 12 which comprises a segment of at least 17 amino acids which is identical to an equal length segment within amino acids 234 to 1791 of SEQ ID NO:2.